Some Implications of the Prion Paradigm: Caveat Denaturor

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To the Editor: The term *prion* connotes an iconoclastic paradigm for an infectious agent afflicting humans and other animals.[1-3] It imputes pathogenicity to the 3-dimensional shape of the PrP^{sc} (prion protein scrapie). The normal cellular protein, PrP^{c}, by exposure to PrP^{sc}, adopts the SC conformation, maintaining a cascade of SC production in vivo. Unlike other self-replicating infectious viruses and bacteria, no unique sequences of DNA or RNA are necessary for this alteration, as the amino acid sequence of PrP^{c} and PrP^{sc} are identical. The SC isoform does exhibit protease resistance as 1 marker. How this conformer modulation occurs is obscure; it may be similar to the "chaperone" functions of some auxiliary proteins that facilitate folding, or to the "epitaxial" outgrowth from a single crystal face, which is exploited in high-performance metallurgy. The propagation of prions is formally similar to that of centrioles, which are aggregates of tubulin that can re-form spontaneously, although they are typically propagated from existing centrioles.[4]

PrP^{c} is genetically regulated, but some mutant forms may be more prone to conformer modulation, either as a spontaneous accident or by exposure to PrP^{sc}, even of another species. Even in the "normal" genotype, the conformeric change might occur spontaneously, however rarely, and thereby account for the rare sporadic cases of nonfamilial Creutzfeldt-Jakob disease. Obviously, it is difficult to exclude contact with prion sources in these cases. Oral ingestion of contaminated meat products is the principal known mechanism of transmission in animals.[3] Inhalation of particles might give easier access to the central nervous system, but this route is not documented.

The prion paradigm implies that a variety of physicochemical stresses generate conformational differences in proteins, and these stresses thus are suspect as potential sources of new prions from PrP^{c} precursors. For example, fluctuations in temperature or pH, salts, detergents, solutes (eg, alcohol, phenol, urea, and guanidine), and foaming are known to cause protein denaturation. Hence, efforts to decontaminate proteinaceous materials by heat-sterilization or with other protein denaturants call for empirical assurance of benefit. The "mad-cow disease" outbreak in the United Kingdom was occasioned by the use of rendered sheep meal as cattle feed.[3] The rendering process was ineffectual in destroying infectivity; it is possible, though untested, that it actually contributed to the problem. Other processes that might denature proteins in vivo include intoxications, infections, burns, or radiation.

Denaturing conditions such as reduction of disulfide bonds or low pH have been used to confer protease resistance on PrP^{c} in vitro.[5] The infectivity of this particular product was not reported. Other efforts to propagate PrP^{sc} in vitro have been inconclusive to date.

Our most pressing need is for reliable in vitro assays for prion activity, either to put these speculations to rest or to provide more secure guidelines for epidemiological inquiry and hygienic precautions. The issues to be examined would include the role of denaturing treatments on the interconversion of PrP^{c} and PrP^{sc} within a species, and the facilitation of species crossing by modification of an existing PrP^{sc}.

Few extant data bear on this proposal. However, a case-control study[6] of environmental risk factors for Creutzfeldt-Jakob disease in Europe found that exposure to heavily processed animal protein (leather products and fertilizer from hooves and horns) was the most conspicuous risk factor, but there was no increased risk for occupational exposure to live animals.

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JAMA 10/13/99 282: 1332-1333

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